

# The effect of stimulus duty cycle and “off” duration on BOLD response linearity

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An ongoing question in functional MRI is precisely how measured signal changes relate to neuronal activity. While this question has been probed using animal models and electrophysiologic measures of neuronal activity, it has also been probed by examining, in humans, the spatial location, magnitude, and temporal dynamics of signal changes to well understood stimuli. With regard to dynamics, several earlier studies have revealed a larger than expected response to brief stimuli, hypothesized to result from nonlinearities in either the hemodynamics or the neuronal activity. In this study, we investigate the linearity of the increase in blood oxygenation level dependent (BOLD) contrast as a function of stimulus duty cycle, as well as the linearity of the decrease in BOLD as a function stimulus “off” duration. These findings not only shed further light on the mechanisms behind BOLD contrast but also give practical information as to what to keep in mind when performing and interpreting event related fMRI experiments. These experiments demonstrated: a) the BOLD signal decrease, on stimulus cessation, was smaller than predicted by a linear system—opposite to what has been reported in the literature associated with a signal increase, and b) the deconvolved event-related BOLD signal is highly dependent on duty cycle (the fraction of time activated vs. non-activated). Several potential mechanisms explaining these dynamics are discussed and modeled. We find that the experimental results are most consistent with a nonlinear neuronal response, but do not rule out significant effects of nonlinear hemodynamic factors, in particular the nonlinear relationship between oxygen extraction fraction and blood flow.

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example, can be strongly affected by larger veins whose oxygenation changes are delayed and downstream from the site of neuronal activity change (Saad et al., 2001). Similarly, the amplitude of measured signal changes associated with changes in the level of neuronal activity is influenced by the complex interaction of above mentioned hemodynamic factors. Making conclusive statements about differences in the level of neuronal activation within brain regions, across brain regions, or between subjects is therefore difficult, requiring that all underlying mechanisms for differences in signal changes are understood and accounted for. One strategy that is pursued to improve this understanding is to investigate the dynamics of the signal changes as they relate to stimulus duration and timing.

Several fMRI studies examining the response to visual and motor stimuli of different durations have demonstrated that the signal behaves in a “non-linear” manner, with short duration stimuli producing responses larger than expected from a linear extrapolation of the response to longer duration stimuli (Boynton et al., 1996; Friston et al., 1998; Vazquez and Noll, 1998). This nonlinearity is most pronounced for stimuli of durations shorter than 2 s. For example, the presentation of a contrast reversing checkerboard for 250 ms can result in a response that is 3–5 times larger than expected from the response to a longer stimulus (Birn et al., 2001). This non-linearity has also been shown to vary across (Birn et al., 2001; Pfeuffer et al., 2003) and within activated regions (Birn et al., 2001). The degree to which this is due to a nonlinear hemodynamic response (i.e., caused by different time constants of blood flow, blood volume, and oxygen extraction), or a nonlinear neuronal response (i.e., greater activation at activity onset than at steady state) is currently unresolved. Nevertheless, there have been preliminary results indicating that both mechanisms play a role—a study showing a strong resemblance between neuronal nonlinearities and these measured BOLD contrast nonlinearities (Bandettini and Ungerleider, 2001), as well as studies demonstrating a difference in the nonlinearity between CBF (as measured by arterial spin labeling (ASL) and BOLD (Miller et al., 2001; Obata et al., 2004).

A few studies have addressed the dynamics of the BOLD response to turning off a stimulus for various durations (Fransson et al., 1999). The return to baseline of BOLD contrast at the

## Introduction

Blood oxygenation level dependent (BOLD) functional MRI (fMRI) signal changes are influenced by the interaction of changes in cerebral blood flow, blood volume, and metabolic rate of oxygen consumption. A central question in fMRI is precisely how these measured hemodynamic signal changes relate to neuronal activity. The location, timing, and amplitude of measured signal changes, for

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cessation of a stimulus may involve different dynamics in changes in blood flow, blood volume, oxidative metabolism, and perhaps neuronal activity, than brief stimulus onsets. Blood flow is at a higher level, and thus changes in flow operate on a different part of the oxygen extraction vs. flow curve (Buxton et al., 1998; Miller et al., 2001). This model predicts that a transient decrease in flow would cause different BOLD signal changes than a transient increase from the resting state. Additionally, blood volume has been shown to decrease with a slower time constant than blood flow changes (Buxton et al., 1998; Mandeville et al., 1999), thus, having a different effect on the BOLD signal magnitude depending on the duration of the OFF period. A study by Fransson et al. (1999) has found that these different dynamics following either stimulation or stimulus cessation are reflected in the BOLD time courses, with post-stimulus undershoots evident for deactivation (following a period of activation) but no overshoot for activation. While the time course of the signal for longer OFF periods has been studied, the linearity of the response during the OFF period has not yet been closely examined.

Further studies have focused on the refractory period of the measured hemodynamic response (Friston et al., 1998; Huettel and McCarthy, 2000, 2001). These studies demonstrate that the response to a second stimulus presented quickly after an initial stimulus is smaller, and somewhat delayed, relative to the response to the initial stimulus. As the rest period between the two stimuli is increased, the response to the second stimulus recovers. Studies have estimated this recovery time, or refractory period, at approximately 4–6 s, and this, too, varies for different brain regions (Huettel and McCarthy, 2001). While neuronal refractory effects have been observed in direct neuronal recording studies (Muller et al., 1999), it is not conclusive if this observed BOLD effect is neurally or hemodynamically mediated.

In this work, we first characterize the BOLD response, specifically its linearity, as a function of stimulus OFF duration. The result of this study, in addition to previous observations of the fMRI response to brief stimuli, suggests a dependence of the estimated hemodynamic response function on the fraction of time in the stimulus versus rest states in a randomized event-related design. In a second study, we characterize the changes in the deconvolved hemodynamic response a function of stimulus duty cycle. Finally, using simulations we examine the mechanisms that may be responsible for the observed BOLD responses to brief stimuli, brief stimulus OFF periods, and varying duty cycle.

## Methods

### Experiments

The goal of the first part of this study is to investigate the linearity of the signal decrease following the cessation of a stimulus. Specifically, we varied the “off” durations in the paradigm, while keeping the “on” duration constant. A contrast reversing checkerboard (8 reversals/s) was presented to subjects for periods of 20 s, alternated with presentations of a neutral gray fixation screen for various durations. The stimulus was alternated with fixation periods of 2, 3, 4, 8, and 16 s interleaved within a single run of 310 images, which was repeated 4 times. An initial stimulus presentation of 30 s allowed the signal to come to a steady

state and helped to identify the baseline of constant stimulation. Additionally, a blocked run consisting of 30 s rest and 30 s visual stimulation was presented.

During this presentation of the stimuli, a series of T2\*-weighted echo-planar images were acquired on a 3 T GE Signa MRI scanner (Waukesha, WI, USA) using a Medical Advances brain-specific quadrature RF coil (Wauwatosa, WI). A volume of eight contiguous axial 5-mm thick contiguous slices spanning the primary visual cortex were acquired every second (Echo-planar imaging, TR: 1 s, TE: 30 ms, FOV: 24 cm, Matrix size: 64 × 64). Five subjects were studied (4 males), and all subjects gave informed consent and scanning was performed under an IRB approved protocol.

Reconstructed images were registered to correct for movement artifacts and further analyzed using the AFNI package (Cox, 1996). One subject was excluded from further study due to excessive motion. In the first study, areas activated by visual stimulation were identified by correlating the measured response in the blocked design with an ideal hemodynamic response (the stimulus design convolved with a Gamma Variate function:  $h(t) = t^{8.6} e^{-t/0.547}$  (Cohen, 1997)). A measure of the linearity was obtained by first computing the ideal linear response to each OFF period (a Gamma Variate function, as mentioned above, convolved with the stimulus timing) and then fitting the amplitudes of these linear responses to the measured response at each OFF period. The resulting fit amplitudes indicate whether the measured responses are larger, equal to, or smaller than a linear prediction. The time courses of responses to varying stimulus OFF periods in each voxel were obtained by averaging the BOLD response across the multiple repetitions. Additionally, to increase statistical power, a spatially averaged response was obtained by averaging the response time courses over the entire activated region.

The goal of the second study was to determine if the findings in the first part of the study generalized to stimulus duty cycle. In the second study of 5 subjects (3 males), a contrast reversing checkerboard was presented in an event-related paradigm with a varying ISI at three different fractions of time spent stimulating: 25%, 50%, and 75% (see Fig. 1). For comparison, a blocked design alternating 30 s periods of a contrast reversing checkerboard with 30-s periods of fixation (50% duty cycle blocked

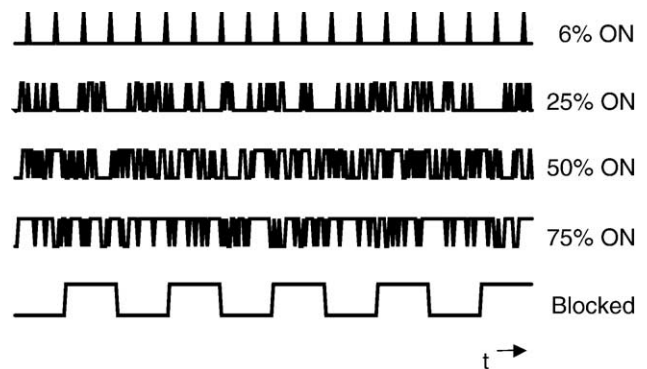


Fig. 1. Five different stimulus timings tested in the second study of responses to different duty cycles: an event-related time course with a 1-s stimulus duration and a constant 16 s inter-stimulus interval; a blocked design with 30 s stimulation alternated with 30 s neutral gray fixation; and event-related designs with a varying ISI and different fraction of the time spent stimulating: 25%, 50%, and 75%.

design), and an event-related time course with a constant ISI of 16 s and a stimulus duration of 1 s (6% duty cycle) were presented.

During this stimulation, a series of 310 axial echo-planar images was acquired, with identical parameters as described above for the first experiment. Resulting images were motion-corrected, and active areas were identified by correlating the response in the blocked design with a reference hemodynamic response. The hemodynamic response function was estimated in each voxel for each of the three event-related designs by deconvolution of the signal from the stimulus input function. For additional comparison and illustration of the effects, the deconvolved impulse responses were convolved with a 30-s boxcar and compared to the averaged BOLD response in the blocked design.

### Simulations

The possibility for both hemodynamic and neuronal mechanisms to account for the nonlinearity of the BOLD response to different stimulus durations has been investigated by earlier studies (Friston et al., 2000; Mechelli et al., 2001; Miller et al., 2001; Obata et al., 2004), but the ability for these mechanisms to explain the observed response to brief OFF periods, as well as variations in stimulus duty cycle, has not yet been closely examined. We therefore simulated both the hemodynamics and neuronal mechanisms that can give rise to the nonlinearities observed in this study.

To investigate the possibility that these nonlinearities are hemodynamic in origin, the BOLD responses to different ON and OFF durations, and different stimulus duty cycles were simulated using the most recent version of the balloon model (Buxton et al., 2004; Obata et al., 2004). A brief summary of the model equations used are given in Appendix A. In this model, hemodynamic nonlinearities can result both from a nonlinear dependence of oxygen extraction on blood flow, or from blood volume changes which are delayed and nonlinearly related to the blood flow change. In order to investigate the contribution of each component independently, four different cases were considered where the oxygen extraction was either a linear or nonlinear function of blood flow, and where blood volume was either allowed to vary or held constant. The linearity was computed from the fit of an ideal response to each BOLD response. This ideal response was determined by convolving an ideal “input” flow (modeled as a gamma variate function convolved with the

stimulus timing) with an exponential impulse response function. This exponential function can be shown analytically to reflect the BOLD response to an impulse of flow in the case that the blood volume is constant. Parameters were chosen to match previously published values (Buxton et al., 2004). In addition, each parameter was allowed to vary individually (with ranges given in Table 1), while the other parameters were held constant at the default value.

A nonlinear relationship between the stimulus and the neuronal response can result from transient neuronal activity following the onset of stimulation, a refractory period during which this initial transient response is diminished, and transient neuronal activity following the cessation of a stimulus. Each of these contributing components was simulated. While an attempt was made to choose reasonable values for the parameters based on existing literature, considerable variability exists depending on the type or population of neurons studied. The goal of this simulation is primarily to demonstrate qualitatively the effect of each contributing component on the linearity of the BOLD response. The initial transient of neuronal activity following the onset of a stimulus (often referred to as an “adaptation” of the response to the stimulus) was simulated by adding a response that has an initial amplitude one half the amplitude of the steady-state neuronal response, an exponential decay to the steady-state level with a decay time of 1.5 s. This amplitude and decay time was chosen to roughly match the local field potential change measured in macaque visual cortex in response to rotating checkerboard, as measured by Logothetis et al. (2001). The refractory period of this transient during the rest state was simulated by modulating the amplitude of the subsequent transient onset response by an exponential recovery with a time constant of 5 s (see Fig. 2a). This value was chosen to produce results consistent with observed BOLD refractory period. The OFF response was simulated by an exponential decay with an initial amplitude of 0.5 (half of the amplitude of the steady state) and a decay time of 0.5 s. Stimulus time courses, and resulting BOLD responses, were generated for the 6 different stimulus timings used in the experimental studies—a blocked design with a task and control period of 30 s, a design with 16 s periods of stimulation and brief rest periods of 1 s, an event-related design with a constant ISI of 16 s, and event-related time courses with varying ISIs and stimulus duty cycles of 25%, 50%, and 75%. These simulated time courses were analyzed in the same manner as the experimental data. The averaged

Table 1

The parameters in the balloon model, the default values, and ranges of values evaluated in the simulation

Parameter	Description	Default value	Range evaluated
$E_0$	Resting oxygen extraction fraction	0.4	0.3–0.6
$v_0$	Resting blood volume fraction	0.03	0.03–0.18
$f_0$	Resting relative blood flow	$0.01 \text{ s}^{-1}$	0.01 s–0.16 s
$\Delta f$	Fractional blood flow change	0.4	–
$\alpha$	Steady-state flow–volume relationship	0.4	0.25–1.0
$\tau_{\text{MTT}}$	Blood mean transit time ( $v_0/f_0$ )	3 s	1.1 s–18 s
$\tau_+$	Viscoelastic time constant (inflation)	20 s	10 s–40 s
$\tau_-$	Viscoelastic time constant (deflation)	20 s	10 s–40 s
$a_1$	Weight for deoxyhemoglobin change	3.7	2.8–5.6
$a_2$	Weight for blood volume change	1.1	0.7–1.9

The effect that each parameter has on the nonlinearity of the BOLD response to varying ON durations, OFF durations, and stimulus duty cycles was tested by varying each parameter within the given range while keeping all other parameters at the default value.

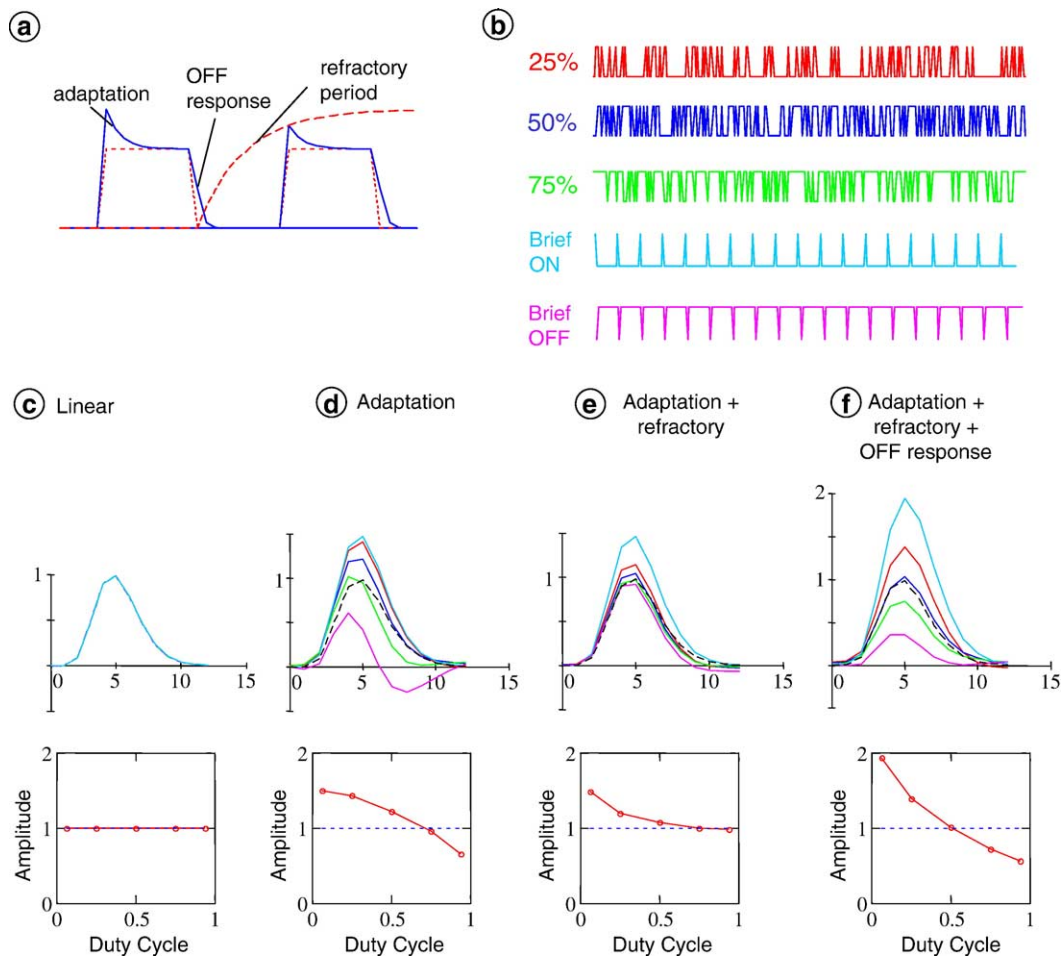


Fig. 2. Simulation results for neuronal sources of nonlinearity. (a) Schematic illustrating the various neural mechanisms considered: an initial overshoot at the start of stimulation, adapting to a steady state (adaptation), firing of some neurons when the stimulus is turned off (OFF response), and a refractory period during which the amplitude of the initial overshoot is diminished by closely preceding stimuli, and recovers during the rest period. (b) Stimulus timings tested in the simulation. (c–f) show the deconvolved responses to the different stimulus paradigms, when considering the combination of various neuronal mechanisms—(c) a linear system; (d) a system with neuronal adaptation; (e) a system with neuronal adaptation and a refractory period; (f) a system with adaptation, a refractory period, and an OFF response. The colors of the curves correspond to the colors of the stimulus paradigms depicted in (b). The dotted line indicates a linear response. Graphs below the deconvolves time courses show the amplitude of the response as a function of stimulus duty cycle (the fraction of the time in the run spent stimulating).

responses to the different stimulus timings were computed by deconvolution, and the amplitudes of these responses were compared to each other to obtain a measure of the linearity. The simulations were then compared with the data obtained in the second study.

## Results

In the first study, the BOLD response behaved in an approximately linear manner for stimulus OFF periods greater than 4 s, but nonlinearly for shorter OFF periods, with signal decreases less than expected from a linear model (see Figs. 3 and 4). Although there is a variability between subjects in the amplitude of the BOLD response to visual stimulation and to the signal decrease in response to each stimulus OFF period, OFF periods of 2 s and 3 s were consistently lower than a linear prediction in all subjects (see Table 2). In one subject, a 2-s stimulus OFF period even resulted in a BOLD signal increase,

rather than a decrease. Also, in a region of the anterior occipital cortex, an increase in the BOLD signal was observed in response to cessation of the stimulus for all stimulus OFF periods. The duration of this positive response was independent of the stimulus OFF period (see Fig. 5).

When the fraction of time spent in the active state compared to the time spent in the control period increased, the deconvolved impulse response function decreased in amplitude. A task–control ratio of 25% resulted in an estimated BOLD response of 1.3%, a task–control ratio of 50% resulted in an estimated BOLD response of 0.97%, and a task–control ratio of 75% resulted in an estimated BOLD response of 0.67% (See Fig. 6). These amplitudes were determined by fitting a gamma-variate function (as defined above) to each deconvolved response. The impulse response function for the 25% stimulation case caused a subsequent overestimation of the response to the 30-s stimulation in the blocked paradigm, similar to previous studies of brief stimulations. The impulse response to 75% stimulation slightly underestimated the response to the blocked



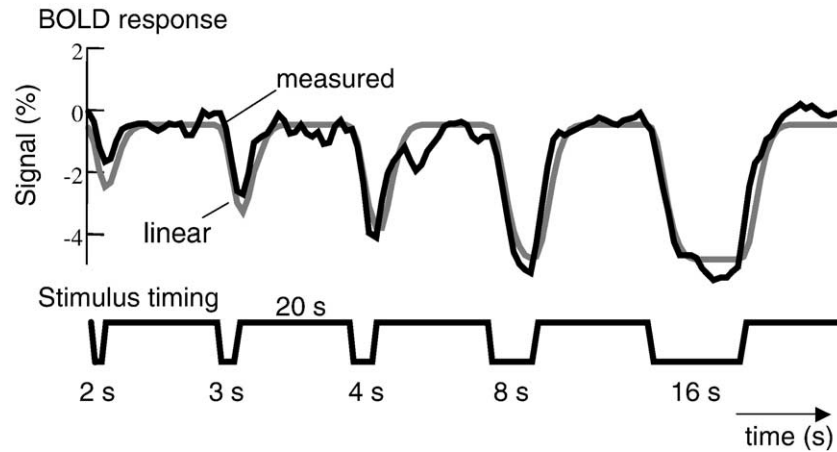


Fig. 3. The BOLD response to a contrast reversing checkerboard presented for periods of 20 s with neutral gray fixation periods of 2, 3, 4, 8, and 16 s. Data are from one representative subject averaged over all significantly activated voxels in the visual cortex. The gray line indicates the response predicted from a linear system, the black line indicates the measured data.

design, exactly what is predicted from the results to the first study which demonstrated smaller signal decreases than expected to brief OFF periods. The averaged BOLD response in event-related design with a constant ISI of 16 s (a task–control ratio of 6%) was 2.1%, larger than the deconvolved responses for the three other stimulus duty cycles studied. Fig. 6c shows the amplitude of each deconvolved response relative to the amplitude of the ideal gamma variate response that would predict a 30-s blocked stimulus. While it would appear from this figure that a stimulus duty cycle of 50%, with an equal number of task and control conditions, would accurately predict the response to a blocked stimulus, the predictions based on the actual deconvolved response (rather than a gamma variate fit to the response) is slightly higher since the deconvolved responses are slightly wider than the ideal gamma variate used in the fit. As a result, the measured response to a 30-s blocked stimulus lies between the predictions from a 50% and a 75% stimulus duty cycle.

Maps of activation from each run are quite similar. Fig. 7 shows the activation amplitude for several voxels for each of the stimulus duty cycles: 25%, 50%, and 75% in one subject. This voxel-by-voxel comparison of activated areas shows that the relative amplitude across space is preserved. Regions with the largest

BOLD signal changes in the blocked design are still the largest for all other stimulation time patterns (see Fig. 7).

#### Simulations

Figs. 8–10 show the simulation results of hemodynamic nonlinearities for four cases that were considered: a full balloon model including oxygen extraction nonlinearities and blood volume changes ( $E(f) = \text{NL}, \Delta V$ ); oxygen extraction nonlinearities alone, with a constant blood volume ( $E(f) = \text{NL}, \Delta V = 0$ ); blood volume changes with a linear dependence of oxygen extraction on flow ( $E(f) = \text{Lin.}, \Delta V$ ); and a case where oxygen extraction was linear and the blood volume was constant ( $E(f) = \text{Lin.}, \Delta V = 0$ ). The degree of the BOLD nonlinearity to varying stimulus ON periods was modulated primarily by the parameters  $\alpha$ , the steady-state flow–volume relationship, and  $\tau_+$ , a viscoelastic time constant describing the rate of the vessel inflation. The linearity to varying OFF periods is modulated primarily by  $\alpha$  and  $\tau_-$ , a viscoelastic time constant describing the rate of vessel deflation. Both nonlinearities are also affected by  $\tau_{\text{MTT}}$ , the mean transit time of the blood through the vessel. Figs. 8f and 9f show the linearity for different values of  $\tau_+$ , while Figs. 8h and 9h shows the linearity for different values of  $\tau_-$ . The arrows indicate the nonlinearities for increasing values of

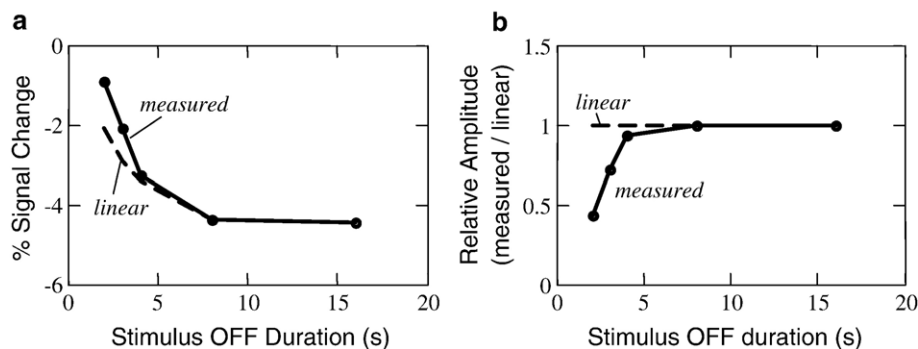


Fig. 4. (a) The amplitude of the BOLD signal decrease, and (b) the amplitude of the BOLD signal decrease relative to a linear system (dashed line) when turning OFF a contrast reversing checkerboard (going to neutral gray fixation) for periods of 2, 3, 4, 8, and 16 s. BOLD signal decreases are smaller than predicted from a linear system.

Table 2

Percent signal changes, averaged over entire activated region in the visual cortex, for 5 different stimulus paradigms—an event-related design with 1 s periods of visual stimulation (contrast-reversing checkerboard) alternated with 15 s of rest; an event-related paradigm with a varying inter-stimulus interval and a stimulus applied for either 25%, 50%, or 75% of the time during the imaging run; and a blocked design with 30 s periods of stimulation alternated with 30 s periods of rest

	Brief ON	25% duty cycle	50% duty cycle	75% duty cycle	Blocked design
Subject 1	1.84	1.65	1.36	1.22	6.58
Subject 2	1.94	1.53	1.13	0.79	4.51
Subject 3	—	1.27	0.89	0.58	4.21
Subject 4	—	1.24	1.1	0.8	3.9
Subject 5	—	1.09	0.83	0.53	3.07
Average	1.89	1.36	1.06	0.78	4.45

Percent signal changes of the event-related paradigms indicate the maximum signal change of a gamma variate fit to the deconvolved response. For the blocked design, the percent signal change indicates the change from baseline (rest) to steady state during stimulation.

$\tau_+$  or  $\tau_-$ . In the case of constant blood volume, none of the parameters that were considered substantially affected the degree of nonlinearity. A balloon model simulation using the default parameters given in Table 1 resulted in a nonlinear BOLD response with larger than expected increases at brief stimulus ON periods, slightly smaller decreases to brief OFF periods (for small  $\tau_-$ ), and smaller responses for higher stimulus duty cycles. When the blood volume was held constant, the BOLD response exhibited a slightly weaker nonlinearity to brief ON periods, but a stronger nonlinearity to brief OFF periods (Figs. 8g and 9g). A linear relationship between OEF and flow in the presence of a constant blood volume resulted in a linear BOLD response (Figs. 8i and 9i). When the blood volume was allowed to vary in response to changes in blood flow, the BOLD response to brief stimulus ON periods was greater than a linear prediction based on the longer duration stimuli (Figs. 8f, h), but the nonlinearity to brief OFF stimuli was reduced (Fig. 9f). Blood volume changes by themselves (with a linear OEF) led to a *greater* than expected decrease at brief OFF periods (relative to a linear prediction from longer OFF periods) for all parameter ranges investigated (Fig. 9h), and resulted in larger responses to higher stimulus duty cycles, opposite to what is observed in the experimental data (Fig. 10g).

The inclusion of neuronal adaptation decreased the response to longer stimuli relative to brief stimuli, decreased the signal decrease associated with brief stimulus OFF periods, and produced a dependence on the stimulus duty cycle with higher duty cycles causing smaller deconvolved responses. The inclusion of a refractory period results in a dampening of the effect of the transient neuronal overshoot, particularly at high stimulus duty cycles. The inclusion of a neuronal OFF response results in a smaller amplitude for high stimulus duty cycles and a large relative amplitude for low stimulus duty cycles.

## Discussion

In the first experimental study, we found that the fMRI signal decreases tend to be sublinear for brief OFF durations, with smaller signal decreases than predicted from a linear system. This observation, combined with earlier observations that brief stimulus ON periods produce larger changes than expected, suggests that the average amplitude of changes for a mixture of brief stimulus ON and OFF periods (such as those that occur in a rapid event-related design) would fall in between the superlinear response to brief ON periods and the sublinear response to brief OFF periods. Moreover, this result predicts that the deconvolved response should show a dependence on the stimulus duty cycle, with designs consisting of fewer stimulations and generally longer control periods leading to an over-estimation of the response to a blocked design (behavior similar to the brief stimulus ON periods), while designs with more frequent stimulations and therefore shorter control periods underestimate the response to a blocked design, as predicted by the study of brief OFF periods. This hypothesized dependence of the deconvolved hemodynamic response on the stimulus duty cycle was indeed observed in the second study.

Explanations for these observations can involve either hemodynamic and/or neuronal mechanisms. First, the measured fMRI signal is a result of a complex interaction of blood flow, blood volume, and oxygen extraction in response to an increased neuronal activity. Secondly, it has been shown that the neuronal response to a visual stimulus is not a simple boxcar shape, but reflects the net sum of a number of neuronal populations, some of which fire more rapidly when the stimulus is first presented (Logothetis et al., 2001; Muller et al., 1999) or turned off (Duysens et al., 1996). Each of these potential hemodynamic and neuronal mechanisms will be briefly examined below.

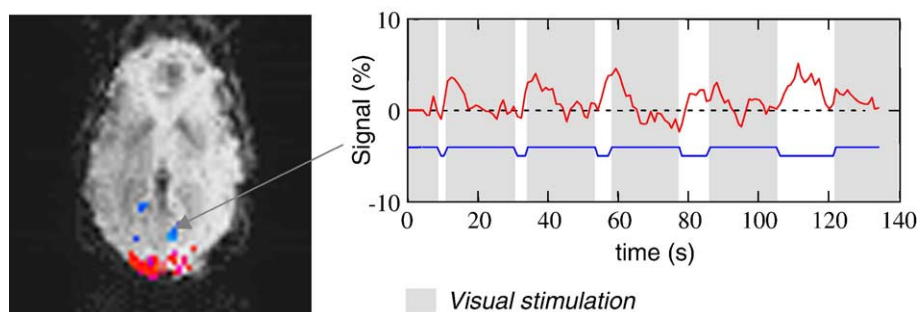


Fig. 5. Regions of the brain (left) and a signal intensity time course (right) showing a signal *increase* when the stimulus is turned off (from contrast-reversing checkerboard to neutral gray fixation), indicated by blue pixels.

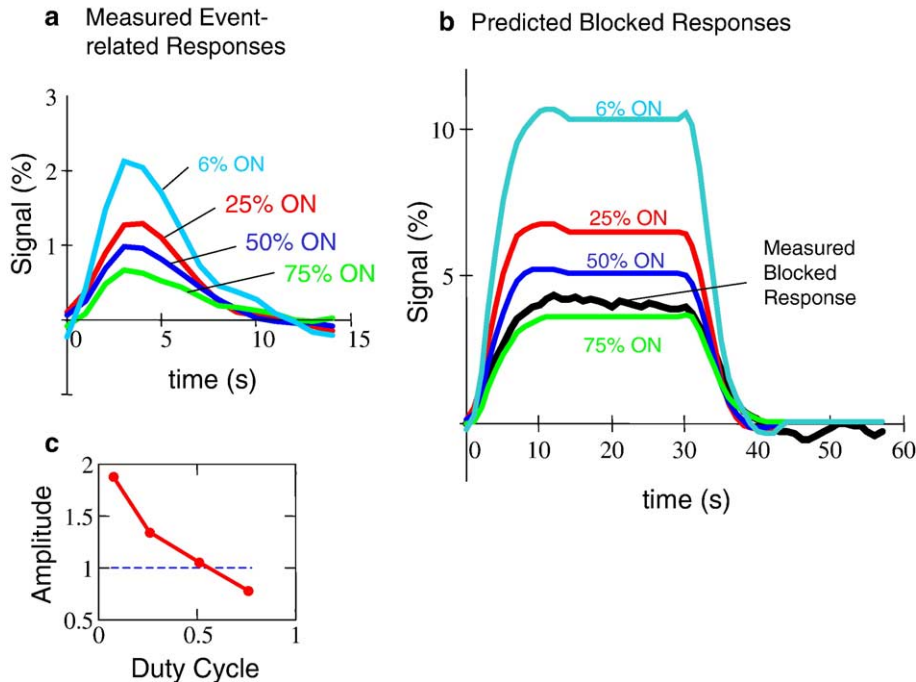


Fig. 6. (a) Deconvolved impulse response functions from the stimulus timings shown in Fig. 1. The amplitude of the estimated response depends on the stimulus timing, with more frequent stimulation resulting in smaller impulse responses. The graph below the deconvolved time courses shows the amplitude of the responses as a function of stimulus duty cycle (the fraction of time in the run spent stimulating). (b) The deconvolved responses are convolved with a stimulus of 30 s duration in order to estimate the response to the blocked stimulus. The response to brief stimuli overestimates the measured response to a 30-s stimulus, whereas the response to more frequent stimulation (75% task–control ratio) underestimates the response to a 30-s stimulus.

### Oxygen extraction

The extraction of oxygen from the blood, and the resulting increase in deoxyhemoglobin back to the blood, is generally not a linear function of blood flow. Under the assumption that an increased oxygen delivery is achieved by an increase in flow velocity, rather than capillary recruitment, the relation between oxygen extraction fraction,  $E(f)$ , and blood flow,  $f$ , is modeled using Eq. (5) (see Appendix). Physiologically, the form of this equation results in part from the decreased ability to extract oxygen from the blood at higher blood flow velocities, and also incorporates the fact that the change in oxygenation cannot be larger than the oxygenation of the inflowing arterial blood (the so-called “BOLD ceiling effect”). The nonlinearities in the BOLD

response observed for both brief ON and brief OFF periods can be, at least partially, explained by this nonlinear dependence of oxygen extraction on flow. Small flow increases from a low flow state result in larger changes in oxygen extraction than small flow decreases from a high flow state (See Fig. 11). In contrast, a linear dependence of oxygen extraction on blood flow would result in a linear BOLD response when the volume is held constant (as seen in Figs. 8i and 9i). While this particular case is mathematically instructive in allowing the different sources of nonlinearity to be isolated, it is not necessarily physiologically relevant. A linear decrease in oxygen extraction as the flow increases would eventually lead to a zero, and then a negative, oxygen extraction. It also ignores the inherent nonlinearity of the BOLD ceiling effect. The BOLD signal can only increase until all of the deoxyhemo-

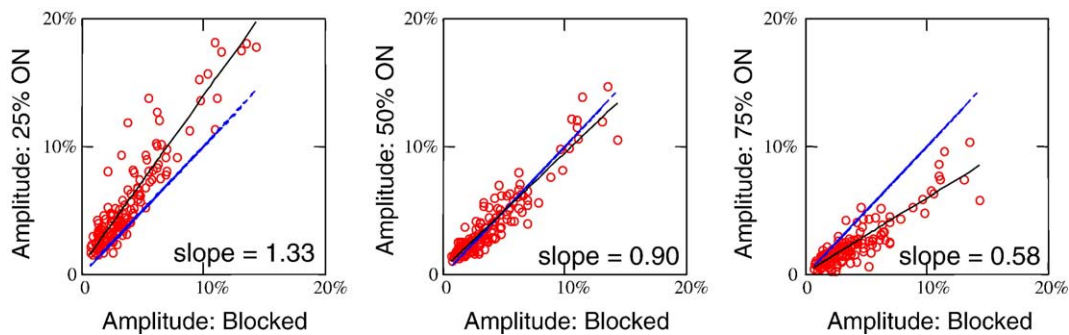


Fig. 7. Graphs comparing the amplitudes of activation between the blocked design and event-related designs at 3 different stimulus duty cycles: 25%, 50%, and 75%. Amplitude values shown are relative to a linear response. Even though the normalized amplitude of the response varies with the stimulation pattern, the relative amplitude across space is preserved. Regions with the largest BOLD signal changes in the blocked design are still the largest for other stimulation time patterns.

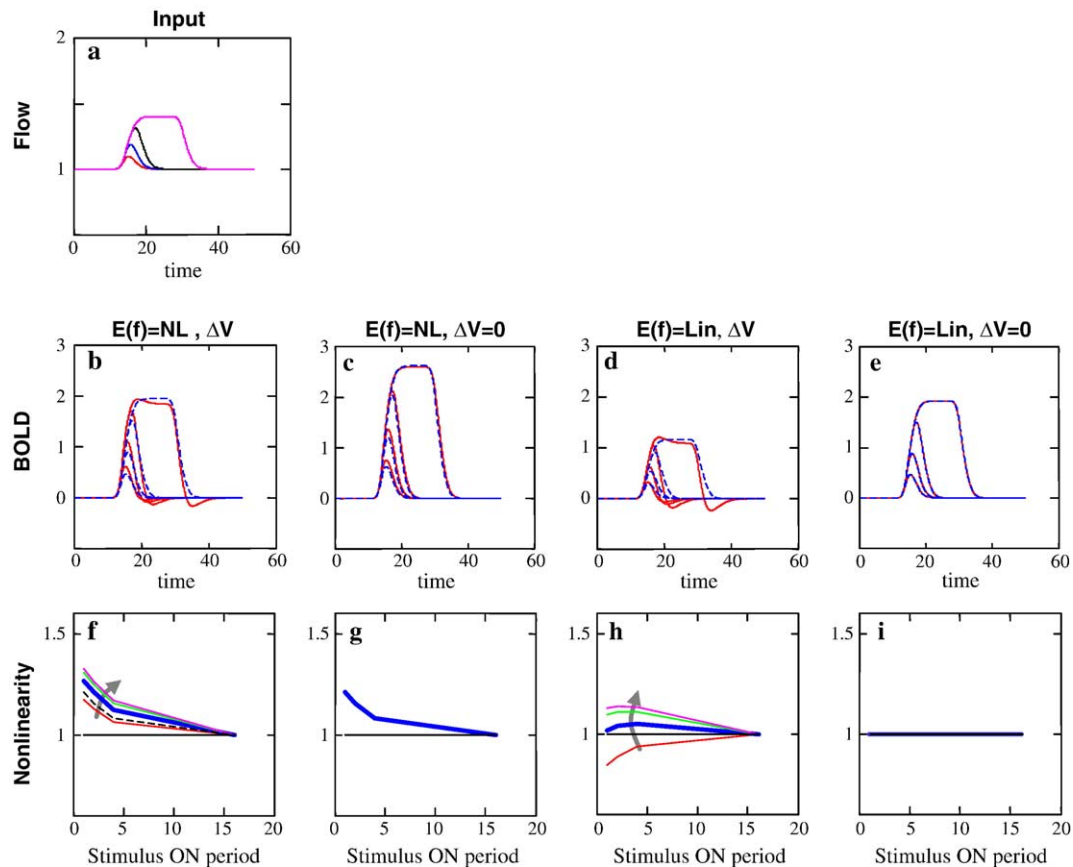


Fig. 8. Simulation of BOLD responses to different stimulus ON periods, using the Balloon model. (a) The flow responses to the stimuli. (b–e) Simulated BOLD responses. The dashed lines represent ideal linear responses, determined by convolving the input flow by an exponential response function. (f–i) The degree of nonlinearity at each stimulus duration, computed by fitting the ideal linear response to the simulated BOLD response. Four cases are simulated: (b, f) a full balloon model including oxygen extraction effects and blood volume changes; (c, g) oxygen extraction effect by themselves with no changes in blood volume; (d, h) blood volume changes with a linear relationship between oxygen extraction fraction and flow; and (e, i) a linear oxygen extraction fraction and no blood volume changes. In (f), different curves represent increasing values of  $\tau_+$ , the viscoelastic time constant for the inflation of the vessel (the arrow indicates the direction the curve shifts with increasing values); the dashed line represents the case of no volume changes for comparison. In (h), different curves represent increasing values of  $\tau_-$ , the viscoelastic time constant for deflation of the vessel.

globin has been removed from the voxel, even if the flow continues to increase. At that point, the BOLD signal, and hence the oxygen extraction, would no longer depend on flow.

Over the physiological range of blood flow changes, it is possible that nonlinearity of the oxygen extraction relative to the blood flow is not sufficient to fully account for the difference in the observed fMRI signal amplitudes. Observed BOLD responses to a 1-s stimulus are often 2–3 times larger than a linear prediction, while the balloon model simulations using the parameter ranges in Table 1 only account for an increased response by a factor up to 1.5 (Birn et al., 2001). Recent studies have also called into question the validity of Eq. (5), since it is derived from steady-state relationship between oxygen extraction and blood flow. This steady-state relationship may not necessarily hold for dynamic changes in blood flow (Mayhew et al., 2001), particularly on the time scale of these observations. In a recent study by Obata et al., the oxygen extraction fraction was allowed to vary freely, not tied to the blood flow by the fixed Eq. (5), in order to explain more complex flow and BOLD dynamics observed in the supplementary motor area. The nonlinear relationship between oxygen extraction fraction and flow can therefore account for some, but perhaps not all, of the observed nonlinearity to both brief stimulations and brief stimulus OFF periods.

#### Blood volume

An increase in neuronal activity results in an increase in both blood flow and blood volume (Belliveau et al., 1991; Buxton et al., 1998; Mandeville et al., 1999). The changes in the blood volume are thought to occur more slowly than changes in blood flow and are hypothesized to reflect the distention of venules and veins in response to the increased blood flow. An increase of blood volume by itself (without an increase in blood flow) would result in an increased pooling of deoxyhemoglobin, and therefore a decrease in the MR signal. In a BOLD fMRI experiment, the MR signal increases in response to neuronal firing, since the flow increase is substantially higher than the increase in blood volume, therefore, washing out the extra deoxyhemoglobin. One mechanism proposed for the nonlinearity of the BOLD response to brief stimuli is that for brief stimulations the blood flow increases are accompanied by delayed increase in blood volume which blunts the MR signal for longer stimulations, but is minimal for brief stimulations, resulting in a nonlinear dependence of the MR signal on stimulus duration (Friston et al., 2000; Vazquez and Noll, 1998).

The simulations in this study show that latent blood volume dynamics can cause larger than predicted responses to brief stimuli (Figs. 8f, h). This nonlinearity results from an initial overshoot in



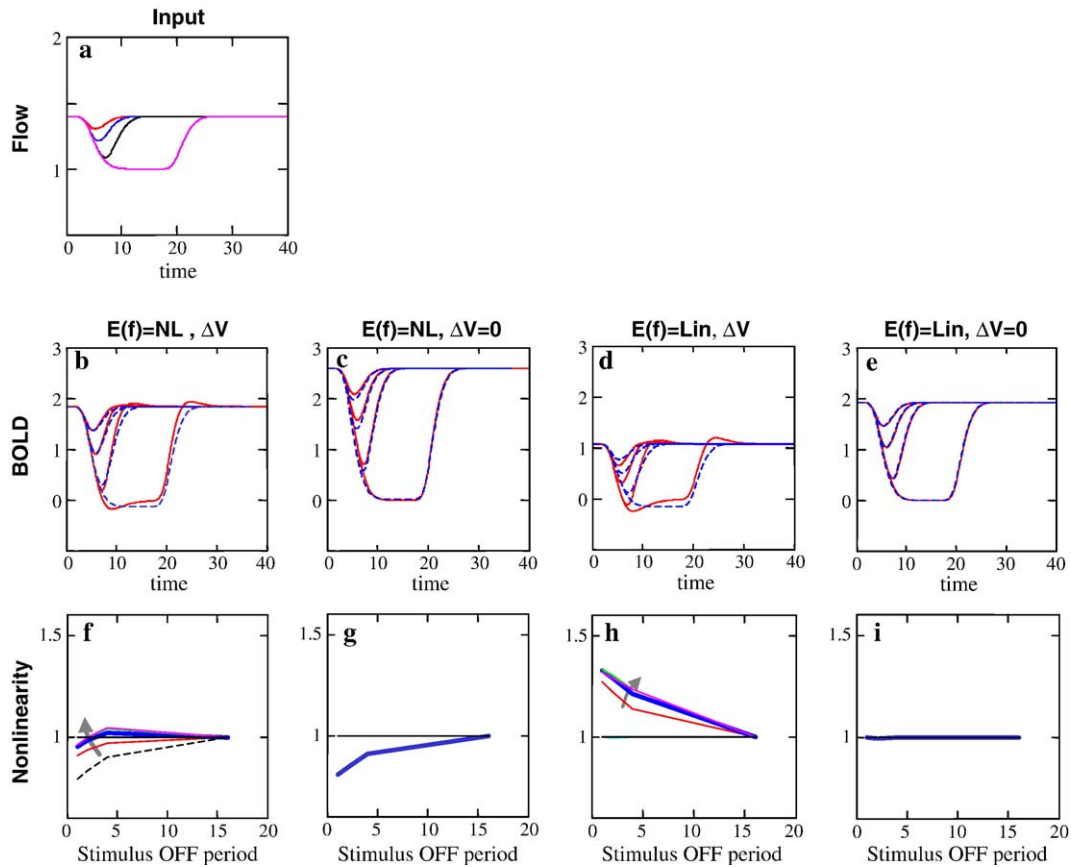


Fig. 9. Simulation of BOLD responses to different stimulus OFF periods, using the Balloon model. Four cases are considered, similar to Fig. 8. In (b–e), dashed lines represent ideal linear responses, while solid red lines reflect the simulated BOLD response. As in Fig. 8, curves in (f) and (h) reflect increasing values of  $\tau_+$  and  $\tau_-$ , respectively. Again, in (f), the dashed black line reflect nonlinearity in the case of a constant blood volume, shown for comparison.

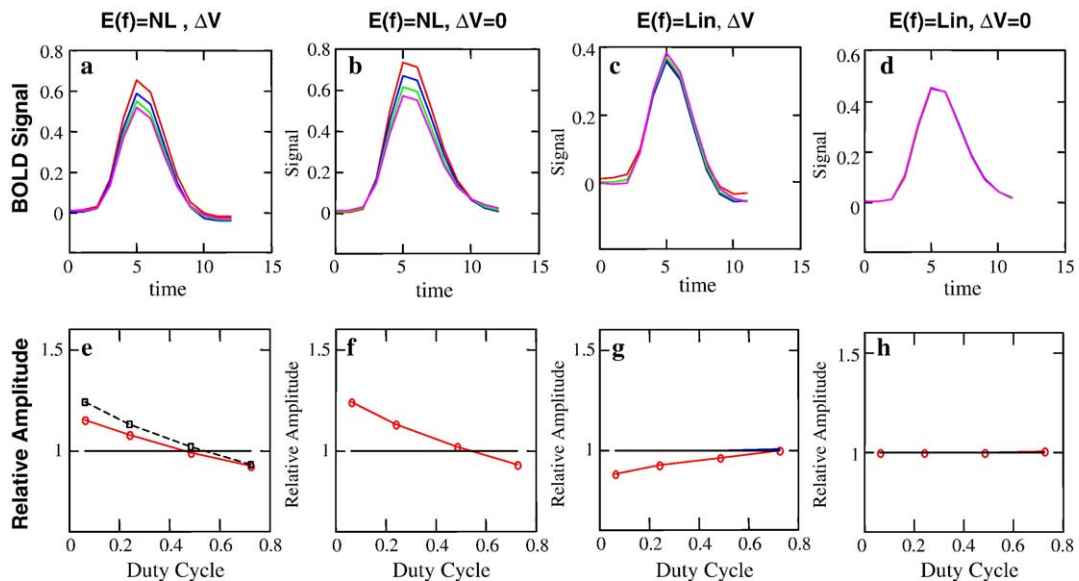


Fig. 10. Simulation of BOLD responses to different stimulus duty cycles. (a–d) show the BOLD responses, (e–h) show the relative amplitudes, where a value of 1 indicates a response that would accurately predict the response to a longer block of stimulation (a “blocked response”) with a linear convolution with the blocked stimulus. As in Figs. 8 and 9, four cases are considered: a full balloon model including both oxygen extraction nonlinearities and blood volume changes, nonlinear oxygen extraction effects by themselves, volume changes in the presence of linear oxygen extraction effects, and linear oxygen extraction with no blood volume changes. In (e), the dashed line indicates the response when volume changes are constant (same as in f), shown to ease comparison.

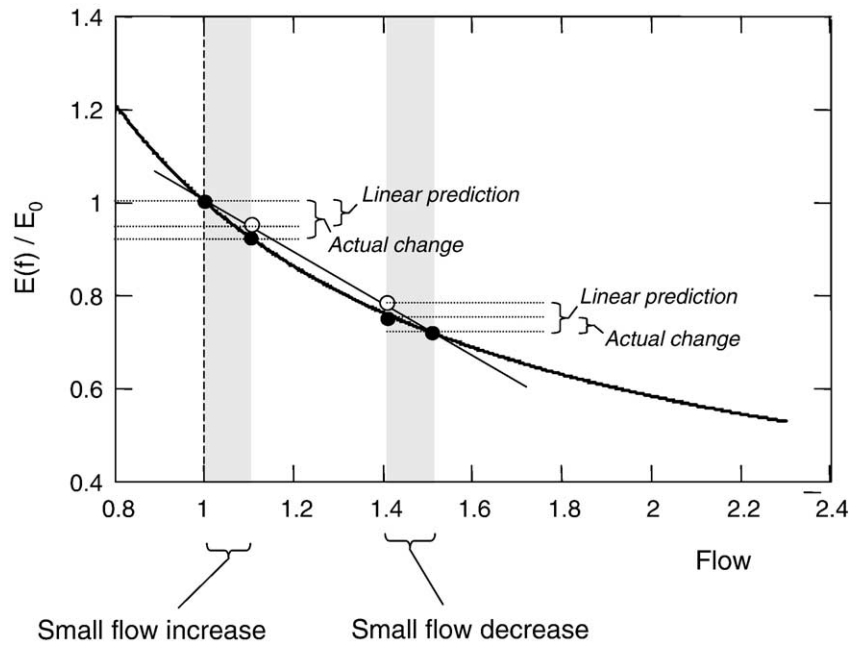


Fig. 11. Relative oxygen extraction fraction ( $E(f)/E_0$ ) as a function of blood flow ( $f$ ). The nonlinear relationship can lead to an oxygen extraction change at small increases from baseline flow that is larger than expected based on a linear prediction from large flow increases. Similarly, a small flow decrease from a high flow state leads to smaller changes than expected based on the linear prediction.

the BOLD signal before the blood volume has increased appreciably. However, latent blood volume dynamics cause a larger decrease than expected from a linear system during the brief OFF period (Figs. 9f, h), opposite to what was actually measured. The reason this occurs is that immediately following the cessation of a stimulus that has been presented for an extended period of time, the blood volume is already elevated and remains elevated while the flow returns to normal, thus driving the BOLD signal down faster. Factors causing signal increases have therefore been reduced while factors causing signal decreases have not. In fact, this very difference in time constants has been used to explain the post-stimulus undershoot that is often observed (Buxton et al., 1998; Friston et al., 2000; Mandeville et al., 1999; Mechelli et al., 2001). Therefore, it would be necessary for blood volume dynamics to be slower than flow changes during the stimulus onset and faster than flow changes during the stimulus cessation period to explain the observed BOLD dynamics. Experimental evidence, as mentioned, suggests that this is not the case.

#### Neuronal adaptation

Single and multi unit electrical recordings of the neuronal response to visual stimulation have shown that a subpopulation of neurons fire more rapidly in response to changes in the stimulus (Albrecht et al., 1984; Bonds, 1991; Logothetis et al., 2001; Maddess et al., 1988; Muller et al., 1999). Since neuronal firing is generally correlated with changes in local field potentials in healthy cortex, these changes are considered in this discussion only as more general changes in neuronal activity, with no attempt to differentiate between the two mechanisms. The activity of a larger population of neurons therefore consists of a burst of activity following the onset of a stimulus which then decays to a lower steady-state level of activity. The neuronal population response to a brief stimulus would therefore reflect predominantly the larger initial neuronal activity, whereas the response to a longer duration

stimulus would reflect more the lower steady-state neuronal response. Greater or lesser fractions of time in the stimulus and control states would result in more or less frequent periods of brief stimulation. A low task vs. control period ratio on average consists of brief stimulation periods separated by longer control periods, whereas a high task–control ratio consists of longer stimulation periods separated by shorter control periods. The estimated impulse response function, deconvolved from the measured signal by using the stimulus timing as the input, would therefore be larger for event-related designs with less frequent stimulations (the 25% duty cycle) (see Fig. 2d). Similarly, the deconvolved response for a task with a 50% duty cycle is smaller than a task with a 75% duty cycle.

An initial overshoot of neuronal activity is likely not the only source of the nonlinearity observed in the BOLD response. The explanation is as follows. In this simulation, a 50% duty cycle results in a deconvolved response larger than predicted from a linear system. As shown, this occurs because the initial transient adds to the measured signal change, and therefore adds to the deconvolved response. A graph of deconvolved response amplitude versus duty cycle shows *increasing* effects for large duty cycles (i.e., a convex curvature of the relationship), *opposite* to what is observed in the data (Fig. 6). Additional mechanisms for the source of the nonlinearities, such as the neuronal refractory period and neuronal OFF response, should therefore be considered.

#### Neuronal refractory period

As described above, the neuronal population can exhibit an initial overshoot in activity that has a decay time constant anywhere from tens of milliseconds to seconds. This transient response recovers slowly when the stimulus is turned off, during a so-called refractory period. As a result, the level of the initial overshoot in activity is larger for longer periods of rest preceding the stimulus. While neuronal adaptation and a neuronal refractory period may be physiologically linked, the two describe different mechanisms.

Adaptation describes how quickly the neuronal response to a stimulus settles into a new state of responsiveness, while the neuronal refractory period describes how long this altered responsiveness is maintained when the stimulus is no longer present. These two time constants need not be the same. Direct recordings in the macaque visual cortex during the presentation of a static grating have found neurons that show transient activity, with an adaptation time constant of about 100 ms. This transient response is diminished following a rest period of only 200 ms, but recovers almost completely after a rest period of 1.75 s (Muller et al., 1999). An event-related design that consists of brief stimulation periods and longer control periods, such as the task–control ratio of 25%, allows for more recovery of the initial transient. The estimated impulse response is therefore more heavily weighted by the initial transient, and overestimates the response to longer duration stimuli. A design with only short control periods, such as a task–control ratio of 75%, does not allow sufficient time for recovery of the initial overshoot, and as a result the estimated impulse response is weighted more heavily by the lower steady-state neuronal activity (see Fig. 2e). The simulated BOLD signal from a neuronal response that incorporates both an initial transient burst of activity and a refractory period of this transient shows both a dependence on stimulus duty cycle, and the predicted amplitude of these responses relative to a blocked design. The simulated response to brief stimulus OFF periods is smaller than a linear prediction, while the response to brief stimulus ON periods larger than a linear prediction, therefore better matching the experimental results. The primary effect of the refractory period is to change the amount by which the deconvolved responses are scaled for different stimulus duty cycles, with larger effects for small duty cycles (see Fig. 2e).

#### Neuronal OFF response

The visual system is highly sensitized to changes in the visual scene. Just as a population of neurons fired more rapidly due to the onset of a stimulus, certain population of neurons have been shown to fire more rapidly when the stimulus is turned off (Duysens et al., 1996). In fact, this is directly observed in the fMRI BOLD signal measured from some brain regions following brief off periods (see Fig. 5). The fMRI signal decrease to brief stimulus OFF periods is therefore less than predicted because a control period (fixation) of 2 s actually corresponds to a much shorter duration of lower neuronal activity.

The inclusion of an OFF response to the simulation incorporating both initial neuronal transients and a refractory period results in a smaller response at higher stimulus duty cycles which therefore underpredicts the response to longer blocked stimuli, more consistent with experimental observations (see Fig. 2f and compare to Fig. 6c). The exact stimulus duty cycle that most accurately predicts the response to a blocked stimulus (a value of 1 in the graphs shown at the bottom of Fig. 2) depends on the relative proportion of neurons exhibiting transient response to stimulus onsets versus offsets. A higher proportion of neurons responding to a stimulus onset, but not an offset, or a larger response to an onset compared to an offset would result in larger deconvolved responses. This may explain the slight overestimation of the blocked response based on the deconvolved response from a 50% duty cycle (Fig. 6b).

While observed nonlinearity of the BOLD response is likely a combination of all of the above hemodynamic and neuronal factors, we demonstrate that it is possible to titrate their relative contributions. Nonlinear neuronal responses to visual stimuli have been demonstrated by direct electrical recordings in cats and non-

human primates (Logothetis et al., 2001; Muller et al., 1999) and are therefore expected to occur in human visual cortex. Furthermore, this nonlinearity can potentially vary for different neuronal populations across and within brain regions. In this study, the linearity of the BOLD response to varying stimulus OFF periods was evaluated for a region of interest (ROI) averaged over all voxels showing a significant correlation with the expected BOLD response, an area that can encompass multiple types of neurons. While all voxels within this activated region showed smaller than predicted responses at brief OFF periods, the degree of this nonlinearity varied. The spatial heterogeneity of this nonlinearity, however, was not specifically investigated in this study. This variability may reflect different proportions of neurons exhibiting either steady-state or transient responses to the stimulus. Prior or prolonged exposure to a stimulus can reduce the influence of these transient responses. It is this adaptation that is hypothesized to be partially responsible for the different deconvolved responses at different stimulus duty cycles, with higher duty cycles allowing for a greater adaptation of these transients. The effect of this adaptation on the linearity of the BOLD response was also investigated in a recent study of the responses within the lateral-occipital cortex to moving visual stimuli (Huettel et al., 2004).

It has also been shown in simulations that hemodynamic parameters can affect the linearity, and it is plausible that these parameters vary across different brain regions. The most clear experimental validation of this has come from simultaneous CBF and BOLD studies which showed a difference in the linearity of the CBF and BOLD responses (Miller et al., 2001; Obata et al., 2004). In addition, studies of the BOLD refractory effect have found that the response to a second stimulus presented a short time (within a few seconds) after the first stimulus is both reduced in amplitude as well as delayed in time (Huettel and McCarthy, 2000). The time constant of this refractory period has been estimated to be several seconds, which is longer than what is expected based on neuronal refractory effects seen in direct electrical recordings of macaque visual cortex (Muller et al., 1999). In addition, the increased latency is difficult to explain using only neuronal mechanisms. In this study, the nonlinearity of the BOLD response to varying stimulus OFF periods was assessed by fitting an ideal hemodynamic response to each voxel's time course. While a shift in the latency of the response can cause a reduction in the estimated amplitude, Fig. 3 clearly shows that the reduced response at brief OFF periods cannot solely be explained by a difference in the latency of the response. Furthermore, an increased delay of the BOLD response following shorter OFF periods should lead to larger than expected decreases, suggesting that the variations in delay observed in studies of the refractory period are not the primary source of the nonlinear response to brief OFF periods.

While the relative contribution of neuronal and hemodynamic factors to the nonlinearity of the BOLD response is unknown, examining the response to brief stimulus OFF periods can provide additional insights. A purely hemodynamic explanation of the nonlinearity, consistent with the balloon model, would result from nonlinearities in the oxygen extraction, the blood volume dynamics, or both. Since the blood volume dynamics predict *greater* decreases in response to brief OFF periods, the nonlinearity introduced by the oxygen extraction must be greater than that introduced by blood volume effects in order to explain the observed responses. Using the ranges of parameters given in Table 1, oxygen extraction effects could not fully account for the 2- to 3-fold increase that is typically observed in response to a 1-

s stimulus duration. Increases in the amount of nonlinearity cannot purely be the result of increased blood volume effects, since this would result in larger than expected signal decreases to brief stimuli. Increases in the nonlinearity, if they are caused by the hemodynamic factors modeled in this simulation, would therefore require a different relation between the oxygen extraction and flow shown in Eq. (5). In fact, this “uncoupling” of oxygen extraction and flow was used by Obata et al. (2004) as one way to explain the different BOLD responses in M1 and SMA with differences in hemodynamic factors. The nonlinearity can also be increased by considering neuronal nonlinearities, such as adaptation, refractory effects, and responses to stimulus offsets. Finally, it is possible that there are additional hemodynamic or neuronal nonlinearities not discussed here that are contributing to the observed BOLD responses.

## Conclusion

We have experimentally determined that a modulation of brief cessations of a visual stimulus produces smaller signal decreases from a steady “on” state than predicted from a linear system. We have also found that the estimated hemodynamic response function depends on the stimulus timing, particularly the fraction of time spent stimulating versus fixation. On a practical level, this is an important finding for the design and analysis of event-related paradigms, in particular when comparing the amplitudes of responses to different tasks. It is important to remember that while deconvolved responses for a task–control ratio of 25% are higher in amplitude than responses to a task–control ratio of 50%, the statistical power involved with estimating that amplitude is still greater for a task–control ratio of 50%. An evenly balanced design is therefore still the most efficient design. If one is comparing the response to different conditions within the same region of the brain, it is generally best to maintain the same duty cycle for each condition to simplify interpretation. While the precise mechanism that is responsible for these nonlinear dynamics cannot be decisively derived from this study, the present evidence of smaller decreases to brief stimulus OFF periods, which is contrary to predictions based on the effects of blood volume, implies that blood volume dynamics, as modeled by the balloon model, are not a dominant source of BOLD nonlinearities. The degree of nonlinearity seen in response to both brief ON and OFF periods suggests either that the relationship between oxygen extraction and flow is more nonlinear than has previously been postulated, that there are additional hemodynamics not accounted for in the balloon model, or that the BOLD responses are the result of a nonlinear neuronal response to the stimulus, including neuronal adaptation and a refractory period. If the latter is indeed the case, then BOLD fMRI closely reflects the underlying neuronal dynamics and can be an accurate method for characterizing neuronal dynamics on a voxel-wise basis or even for mapping relative proportions of specific neuronal populations within each voxel.

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## Appendix A

The Balloon model (Buxton et al., 1998, 2004) is a mathematical description of the dynamics of blood flow, blood volume, and oxygen extraction which in combination produce BOLD signal changes. The observed signal is considered to be a sum of intravascular and extravascular components, which simplify to

$$\frac{\Delta S}{S} \approx V_0 [a_1(1 - q) + a_2(1 - v)] \quad (1)$$

where  $V_0$  is the resting blood volume fraction,  $q$  denotes the relative amount of deoxyhemoglobin ( $q = 1$  at rest),  $v$  denotes the relative blood volume ( $v = 1$  at rest), and  $a_1$  and  $a_2$  are dimensionless parameters that depend on a variety of experimental and physiological factors. The dynamics of the BOLD signal change in response to changes in flow is described by a set of differential equations,

$$\frac{dq}{dt} = \frac{1}{\tau_{MTT}} \left[ \frac{F_{in}(t) \frac{E(f)}{E_0} - F_{out}(v, t) \frac{q(t)}{v(t)}}{1 + \frac{1}{2\tau_{MTT}} \frac{F_{avg}(v, t)}{v_{avg}(t)}} \right] \quad (2)$$

$$\frac{dv}{dt} = \frac{1}{\tau_{MTT}} \left[ \frac{F_{in}(t) - F_{out}(v, t)}{1 + \frac{1}{2\tau_{MTT}} \frac{df}{dv} \frac{\tau_{\pm}}{\sqrt{v(t)}}} \right] \quad (3)$$

where  $f$  is the relative blood flow,  $\tau_{MTT}$  is the mean transit time of the blood through the vessel,  $E_0$  is the resting oxygen extraction fraction, and  $\tau_+$  and  $\tau_-$  are viscoelastic time constants describing the inflation and deflation of the vessel, respectively.  $F_{in}(t)$  is the blood flow into the vessel, while  $F_{out}(v, t)$  describes the blood flow out of the vessel, which is a function of the blood volume,

$$F_{out}(v) = v^{\frac{1}{\alpha}} \quad (4)$$

also known as Grubb’s law. While this relationship was determined empirically from different steady-state levels of blood flow, the viscoelastic parameters mentioned above allow for deviations from this relationship as the balloon is inflating or deflating.  $F_{avg}(t)$  is an average of the blood flow into the vessel and out of the vessel, while  $v_{avg}(t)$  is the average blood volume.  $E(f)$  is a function that describes the oxygen extraction at different blood flow levels (Buxton and Frank, 1997),

$$E(f) = 1 - (1 - E_0)^{\frac{1}{f}} \quad (5)$$

This equation incorporates the heart of BOLD imaging—the fact that oxygen extraction, and therefore the total amount of deoxy-hemoglobin, decreases with increasing blood flow.

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